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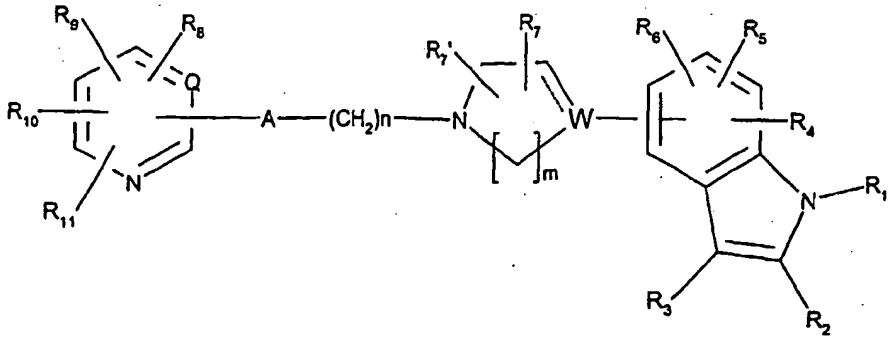
(54) Title: NOVEL INDOLE DERIVATIVES



(I)

(57) Abstract: A heteroaryl derivative having the formula (I). The compounds of the invention are considered useful for the treatment of affective disorders such as general anxiety disorder, panic disorder, obsessive compulsive disorder, depression, social phobia and eating disorders, and neurological disorders such as psychosis.

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Novel indole derivatives.

The present invention relates to novel heteroaryl derivatives potently binding to the 5-HT_{1A} receptor, pharmaceutical compositions containing these compounds and the use thereof for the treatment of certain psychiatric and neurological disorders. Many of the compounds of the invention have also potent serotonin reuptake inhibition activity and are thus considered particularly useful for the treatment of depression.

Furthermore, many compounds of the invention have also effect at dopamine D_3 and D_4 receptors and are considered to be useful for the treatment of psychosis.

Background Art

Clinical and pharmacological studies have shown that 5-HT_{1A} agonists and partial agonists are useful in the treatment of a range of affective disorders such as generalised anxiety disorder, panic disorder, obsessive compulsive disorder, depression and aggression.

It has also been reported that 5-HT_{1A} ligands may be useful in the treatment of ischaemia.

An overview of 5-HT_{1A} antagonists and proposed potential therapeutic targets for these antagonists based upon preclinical and clinical data are presented by Schechter et al. *Serotonin* **1997**, Vol.2, Issue 7. It is stated that 5-HT_{1A} antagonists may be useful in the treatment of schizophrenia, senile dementia, dementia associated with Alzheimer's disease, and in combination with SSRI antidepressants also to be useful in the treatment of depression.

5-HT reuptake inhibitors are well-known antidepressant drugs and useful for the treatment of panic disorders and social phobia.

The effect of combined administration of a compound that inhibits serotonin reuptake and a 5-HT_{1A} receptor antagonist has been evaluated in several studies (Innis, R.B. et al. *Eur. J. Pharmacol.* **1987**, *143*, p 195-204 and Gartside, S.E. *Br. J. Pharmacol.* **1995**, *115*, p 1064-1070, Blier, P. et al. *Trends Pharmacol. Sci.* **1994**, *15*, 220). In these studies it was found

that combined 5-HT_{1A} receptor antagonists and serotonin reuptake inhibitors would produce a more rapid onset of therapeutic action.

Dopamine D_4 receptors belong to the family of dopamine D_2-like receptors which is considered to be responsible for the antipsychotic effects of neuroleptics. Dopamine D_4 receptors are primarily located in areas of the brain other than *striatum*, suggesting that dopamine D_4 receptor ligands have antipsychotic effect and are devoid of extrapyramidal activity.

Accordingly, dopamine D_4 receptor ligands are potential drugs for the treatment of psychosis and positive symptoms of schizophrenia and compounds with combined effects at dopamine D_4, and serotonergic receptors may have the further benefit of improved effect on negative symptoms of schizophrenia, such as anxiety and depression, alcohol abuse, impulse control disorders, aggression, side effects induced by conventional antipsychotic agents, ischaemic disease states, migraine, senile dementia and cardiovascular disorders and in the improvement of sleep.

Dopamine D_3 receptors also belong to the family of dopamine D_2-like receptors. D_3 antagonistic properties of an antipsychotic drug could reduce the negative symptoms and cognitive deficits and result in an improved side effect profile with respect to EPS and hormonal changes.

Accordingly, agents acting on the 5-HT_{1A} receptor, both agonists and antagonists, are believed to be of potential use in the therapy of psychiatric and neurological disorders and thus being highly desired. Furthermore, antagonists, at the same time having potent serotonin reuptake inhibition activity and/or D_4 and/or D_3 activity, may be particularly useful for the treatment of various psychiatric and neurological diseases.

Previously, closely related structures have been reported:

WO 9955672 discloses a general formula in which indole derivatives having 5-HT_{1A} receptor and D_2 receptor affinity are included

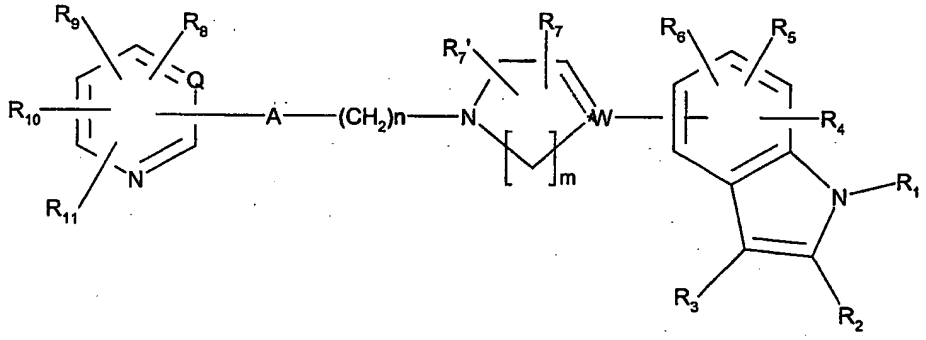
EP 900792 discloses a general formula in which indole derivatives are embraced as 5-HT_{1A} and 5-HT_{1D} as well as D_2 receptor ligands.

It has now been found that a class of indole derivatives is particularly useful as 5-HT_{1A} ligands. Furthermore, it has been found that many of these compounds have other highly beneficial properties as e.g. potent serotonin reuptake inhibition activity and/or affinity for the D_4 receptor.

Summary of the invention

The invention comprises the following:

A compound represented by the general formula I



I

wherein

A represents O or S;

n is 2, 3, 4, 5, 6, 7, 8, 9 or 10;

m is 2 or 3;

W represents N, C or CH;

Q represents N, C or CH;

and the dotted line represents an optional bond;

R^1 represents hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, aryl-C_{1-6}-alkyl or acyl;

R^2, R^3, R^4, R^5 and R^6 independently represent hydrogen, halogen, cyano, nitro, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylsulfanyl, C_{1-6} alkylsulfonyl, hydroxy, hydroxy-C_{1-6}-alkyl, C_{1-6}-

alkoxycarbonyl, acyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, trifluoromethyl, trifluoromethoxy, $NR^{15}R^{16}$ wherein R^{15} and R^{16} independently represent hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or phenyl; or R^{15} and R^{16} together with the nitrogen to which they are attached form a 5- or 6-membered ring optionally containing one further heteroatom;

R^7 and $R^{7'}$ independently represent hydrogen or C_{1-6}-alkyl or may together form a bridge consisting of two or three methylene groups;

R^8, R^9, $R^{10}$and R^{11} are each independently selected from hydrogen, halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, phenyl, thiophenyl, C_{1-6}-alkoxy, C_{1-6}-alkylsulfanyl, C_{1-6}-alkylsulfonyl, hydroxy, formyl, acyl, acylamino, aminocarbonyl, C_{1-6}-alkoxycarbonylamino, aminocarbonylamino, C_{1-6}-alkylaminocarbonylamino and di(C_{1-6}-alkyl)amino-carbonylamino, $NR^{13}R^{14}$ wherein R^{13} and R^{14} independently represent hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or phenyl; or R^{13} and R^{14} together with the nitrogen to which they are attached form a 5- or 6-membered carbocyclic ring optionally containing one further heteroatom;

its enantiomers, and a pharmaceutically acceptable acid addition salt thereof.

The invention also relates to a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier or diluent.

In a further embodiment, the invention relates to the use of a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of a disorder or disease responsive to the inhibition of serotonin uptake and antagonism of 5-HT_{1A} receptors.

In a further embodiment, the invention relates to the use of a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of a disorder or disease responsive to the combined effect of 5-HT_{1A} receptors and dopamine D_4 receptors.

In particular, the invention relates to the use of a compound according to the invention or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of affective disorders such as general anxiety disorder, panic disorder, obsessive compulsive disorder, depression, social phobia and eating disorders; other psychiatric disorders such as psychosis and neurological disorders.

In still another embodiment, the present invention relates to a method for the treatment of a disorder or disease of living animal body, including a human, which is responsive to the inhibition of serotonin uptake and antagonism of 5-HT_{1A} receptors comprising administering to such a living animal body, including a human, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof.

In still another embodiment, the present invention relates to a method for the treatment of a disorder or disease of living animal body, including a human, which is responsive to the effect of 5-HT_{1A} and D_4 receptors comprising administering to such a living animal body, including a human, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof.

Due to their combined antagonism of 5-HT_{1A} receptors and serotonin reuptake inhibiting effect, the compounds of the invention are considered particularly useful as fast onset of action medicaments for the treatment of depression. The compounds may also be useful for the treatment of depression in patients who are resistant to treatment with currently available antidepressants.

The compounds of the invention have high affinity for the 5-HT_{1A} and D_4 receptors. Accordingly, the compounds of the invention are considered useful for the treatment of affective disorders such as general anxiety disorder, panic disorder, obsessive compulsive disorder, depression, social phobia and eating disorders; other psychiatric disorders such as psychosis and neurological disorders.

Detailed description of the invention

In preferred embodiments of the invention, n is 2, 3 or 4

In preferred embodiments of the invention, W represents N;

In preferred embodiments of the invention, Q represents N;

In preferred embodiments of the invention, Q represents C or CH;

In preferred embodiments of the invention, R^7 and $R^{7'}$ are both hydrogen;

In preferred embodiments of the invention, R^1 is hydrogen;

In preferred embodiments of the invention, R^2, R^3, R^4, R^5 and R^6 represent hydrogen;

In preferred embodiments of the invention, R^8, R^9, R^{10} and R^{11} independently represent hydrogen, halogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, CN, CF_3, OCF_3, NH_2, $NR^{13}R^{14}$ wherein R^{13} and R^{14} independently represent hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or phenyl; or R^{13} and R^{14} together with the nitrogen form a piperidine or pyrrolidine;

In more preferred embodiments of the invention, R^8, R^9, R^{10}, R^{11} and R^{12} independently represent methyl, cyclopropyl, trifluoromethyl, cyano, chloro, bromo, piperidinyl, phenyl;

In a preferred embodiment of the invention, the compounds of formula I as described above are:

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}-4,6-dimethylnicotinonitrile, 1a

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}-6-(thiophen-2-yl)-4-trifluoromethylnicotinonitrile, 1b

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}pyridine, 1c

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}-6-methylnicotinonitrile, 1d

3-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-2-chloropyridine, 1e

3-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-2-bromopyridine, 1f

3-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-2-methylpyridine, 1g

3-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-5-chloropyridine, 1h

2-{4-[4-(1H-Indol-4-yl)piperazin-1-yl]butylsulfanyl}-5-trifluoromethylpyridine, 1i

2-{4-[4-(1H-Indol-4-yl)piperazin-1-yl]butylsulfanyl}-4,6-dimethylnicotinonitrile, 1j

2-{3-[4-(1H-Indol-4-yl)piperazin-1-yl]propylsulfanyl}-5-trifluoromethylpyridine, 1k

2-{3-[4-(1H-Indol-4-yl)piperazin-1-yl]propylsulfanyl}-4,6-dimethylnicotinonitrile, 1l

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}-6-methylnicotinamide, 2a

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}nicotinonitrile, 2b

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}-4-methylpyridine, 2c

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}-4-methyl-6-(piperidin-1-yl)nicotinonitrile, 2d

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}-4-trifluoromethyl-6-cyclopropylnicotinonitrile, 2e

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}-3-methanesulfonyl-4-methyl-6-phenylpyridine, 2f

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}nicotinonitrile, 2g

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-4-methylpyridine, 2h

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-6-methylnicotinamide, 2i

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-4-methyl-6-(piperidin-1-yl)nicotinonitrile, 2j

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-4-trifluoromethyl-6-cyclopropylnicotinonitrile, 2k

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-3-methanesulfonyl-4-methyl-6-phenylpyridine, 2l

6-Chloro-2-{2-[4-(1H-indol-4-yl)piperazin-1-yl]ethylsulfanyl}-4-methylnicotinonitrile, 2m

6-Chloro-5-fluoro-2-{2-[4-(1H-indol-4-yl)piperazin-1-yl]ethylsulfanyl}nicotinonitrile, 2n

4,6-Dimethyl-2-{2-[4-(1H-indol-4-yl)piperazin-1-yl]ethylsulfanyl}pyrimidine, 2o

5-Cyano-4-{2-[4-(1H-indol-4-yl)piperazin-1-yl]ethylsulfanyl}pyrimidine, 2p

5-Cyano-4-{2-[4-(1H-indol-4-yl)piperazin-1-yl]ethylsulfanyl}-6-methylsulfanyl-2-phenylpyrimidine, 2q

5-Ethyl-2-{2-[4-(1H-indol-4-yl)piperazin-1-yl]ethylsulfanyl}pyrimidine, 2r

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}-4-trifluoromethylpyrimidine, 2s

or a pharmaceutical acceptable salt thereof.

Definition of substituents etc.

The term C_{1-6} alkyl refers to a branched or linear alkyl group having from one to six carbon atoms inclusive, including, but not limited to, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl and 2-methyl-1-propyl.

Similarly, C_{2-6} alkenyl and C_{2-6} alkynyl, respectively, designate such groups having from two to six carbon atoms inclusive wherein the groups are having at least one double bond or triple bond, respectively.

The terms C_{1-6}-alkoxy, C_{1-6} alkylsulfanyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylamino, C_{1-6} alkylcarbonyl, hydroxy-C_{1-6}-alkyl etc. designate such groups in which the C_{1-6} alkyl is as defined above.

The term C_{3-8} cycloalkyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms, including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

The term aryl refers to a carbocyclic aromatic group, such as phenyl, naphthyl, in particular phenyl. As used herein, aryl may be substituted one or more times with halogen, nitro, cyano, trifluoromethyl, C_{1-6}-alkyl, hydroxy and C_{1-6}-alkoxy.

Halogen means fluoro, chloro, bromo or iodo.

As used herein, the term acyl refers to formyl, C_{1-6}-alkylcarbonyl, arylcarbonyl, aryl-C_{1-6}-alkylcarbonyl wherein the aryl is as defined above, C_{3-8}-cycloalkylcarbonyl or a C_{3-8}-cycloalkyl-C_{1-6}alkyl-carbonyl group.

The term aminocarbonyl means –CO-amino wherein amino is defined as above.

The term acylamino means a group of the formula –NHCOH, –NHCO-C_{1-6}-alkyl, -NHCO-aryl, -NHCO-C_{3-8}-cycloalkyl, -NHCO-C_{3-8}-cycloalkyl-C_{1-6}-alkyl, wherein the alkyl, cycloalkyl and aryl are as defined above.

The terms aminocarbonylamino, C_{1-6}-alkylaminocarbonylamino and di(C_{1-6}-alkyl)aminocarbonylamino mean a group of the formula $NHCONH_2$, –$NHCONHC_{1-6}$-alkyl, NHCON(di-C_{1-6}-alkyl), respectively.

The acid addition salts of the invention are preferably pharmaceutically acceptable salts of the compounds of the invention formed with non-toxic acids. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

Further, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

Some of the compounds of the present invention contain chiral centres and such compounds exist in the form of isomers (e.g. enantiomers). The invention includes all such isomers and any mixtures thereof including racemic mixtures.

Racemic forms can be resolved into the optical antipodes by known methods, for example by separation of diastereomeric salts thereof with an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optically active matrix. Racemic compounds of the present invention can also be resolved into their optical antipodes, e.g. by fractional crystallization of d- or l- (tartrates, mandelates or camphorsulphonate) salts for example. The compounds of the present invention may also be resolved by the formation of diastereomeric derivatives.

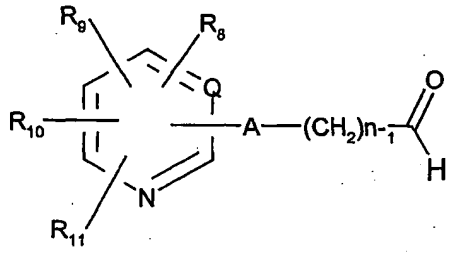
Additional methods for the resolution of optical isomers, known to those skilled in the art, may be used. Such methods include those discussed by J. Jaques, A. Collet and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optically active compounds can also be prepared from optically active starting materials.

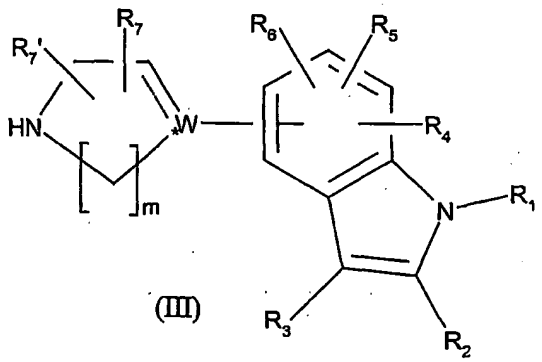
Finally, formula (I) includes any tautomeric forms of the compounds of the invention.

The compounds of the invention can be prepared by one of the following methods comprising:

a) treating a compound of formula (II) with a compound of formula (III) in the presence of a reducing agent .



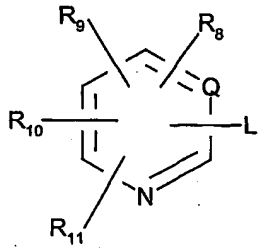
(II)



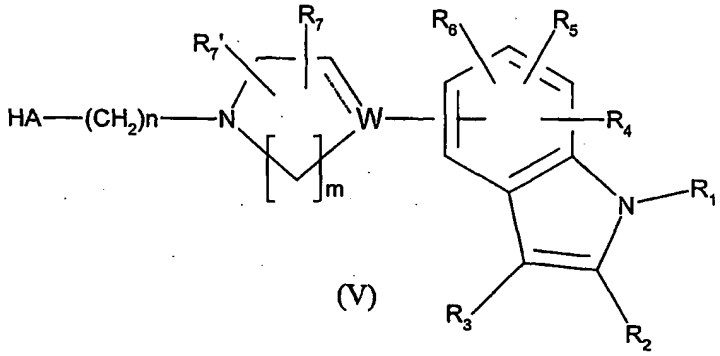
(III)

wherein n, m, $R^1 - R^{11}$, Q, W, A and the dotted line are as defined above;

b) treating a compound of formula (IV) with a compound of formula (V) in the presence of an appropriate base



(IV)



(V)

wherein L is a suitable leaving group such as e.g. chloro and n, m, $R^1 - R^{12}$, Q, W, A and the dotted line are as defined above.

The compounds of formula (I) are isolated as the free base or in the form of a pharmaceutically acceptable salt thereof.

The reductive amination according to method a) is preferably carried out in an inert organic solvent such as dimethylformamide or tetrahydrofuran in the presence of a reducing agent, e.g. triacetoxyborohydride, at room temperature.

The arylation according to method b) is conveniently performed in an inert organic solvent such as dimethylformamide in the presence of a base (eg potassium tert-butoxide) at a temperature in the range of 40-100 °C, preferably in the range of 40-80 °C and most preferred around 50 °C.

Preparation of indolyl piperazines and tetrahydropyridyl piperazines of formula (III) is described in WO 9967237. Aldehydes of formula (II) are prepared as described in the Examples below. Alcohols and mercaptans of formula (V) are prepared as described in the Examples below. The starting chloropyridines of formula (IV) are commercially available or made by methods well-described in the literature

The following examples will illustrate the invention further. They are, however, not to be construed as limiting.

Examples

Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. Analytical LC-MS data were obtained on a PE Sciex API 150EX instrument equipped with IonSpray source (method D) or heated nebulizer (APCI, methods A and B) and Shimadzu LC-8A/SLC-10A LC system. The LC conditions [30 X 4.6 mm YMC ODS-A with 3.5 μm particle size] were linear gradient elution with water/acetonitrile/trifluoroacetic acid (90:10:0.05) to water/acetonitrile/trifluoroacetic acid (10:90:0.03) in 4 min at 2 mL/min. Purity was determined by integration of the UV trace (254 nm). The retention times R_t are expressed in minutes.

Mass spectra were obtained by an alternating scan method to give molecular weight information. The molecular ion, MH+, was obtained at low orifice voltage (5-20V) and fragmentation at high orifice voltage (100V).

Preparative LC-MS-separation was performed on the same instrument. The LC conditions (50 X 20 mm YMC ODS-A with 5 μm particle size) were linear gradient elution with water/acetonitrile/trifluoroacetic acid (80:20:0.05) to water/acetonitrile/trifluoroacetic acid (10:90:0.03) in 7 min at 22.7 mL/min. Fraction collection was performed by split-flow MS detection.

^{1}H NMR spectra were recorded at 500.13 MHz on a Bruker Avance DRX500 instrument or at 250.13 MHz on a Bruker AC 250 instrument. Deuterated chloroform (99.8%D) or dimethyl sulfoxide (99.9%D) were used as solvents. TMS was used as internal reference standard. Chemical shift values are expressed in ppm-values. The following abbreviations are used for multiplicity of NMR signals: s=singlet, d=doublet, t=triplet, q=quartet, qui=quintet, h=heptet, dd=double doublet, dt=double triplet, dq=double quartet, tt=triplet of triplets, m=multiplet, b=broad singlet. NMR signals corresponding to acidic protons are generally omitted. Content of water in crystalline compounds was determined by Karl Fischer titration. Standard workup procedures refer to extraction with the indicated organic solvent from proper aqueous solutions, drying of combined organic extracts (anhydrous $MgSO_4$ or Na_2SO_4), filtering and evaporation of the solvent *in vacuo*. For column chromatography silica gel of type Kieselgel 60, 230-400 mesh ASTM was used. For ion-exchange chromatography (SCX, 1 g, Varian Mega Bond Elut®, Chrompack cat. no. 220776). Prior use the SCX-columns were pre-conditioned with 10% solution of acetic acid in methanol (3 mL).

Example 1

4,6-Dimethyl-2-(2-oxo-ethylsulfanyl)-nicotinonitrile

4,6-Dimethyl-2-mercaptonicotinonitrile (3.0 g) was dissolved in DMF (40 mL) and a solution of potassium *tert*-butoxide (19.2 mL; 1 M) in *tert*-butanol added. The mixture was stirred for 10 min, added dropwise to a solution of bromoacetaldehyd-dimethylacetal (3.2 g) in DMF (10 mL) and stirred over night at 70 °C. The mixture was poured on water and extracted with ethyl acetate, the combined organic phases dried and evaporated to give an oil (5.3 g) which was dissolved in dioxane (40 mL), HCl (20 mL; 3 M) was added and the mixture was stirred at 30 °C for 2 h. $NaHCO_3$ was added until pH reached 5-6, the mixture was extracted with ethyl acetate, the combined organic phases dried with Na_2SO_4 and

evaporated to give the title compound as an oil (2.9 g). ^{1}H NMR ($CDCl_3$) : δ 2.45 (s, 6H); 3.35 (d, 2H); 6.85 (s, 1H); 9.55 (t, 1H).

2-{2-[4-(1H-Indol-4-yl-piperazin-1-yl]ethylsulfanyl}-4,6-dimethylnicotinonitrile **1a.**

4,6-Dimethyl-2-(2-oxo-ethylsulfanyl)nicotinonitrile (2.9 g) was dissolved in 1,2-dichloroethane (150 mL), a solution of 1-(1*H*-indol-4-yl)piperazine (2.4 g) in DMF (150 mL) was added, sodium triacetoxyborohydride (14.9 g) was then added followed by stirring for 2 h. The mixture was poured on water and Na_2CO_3 added until pH reached 7-8. The mixture was extracted with ethyl acetate, the combined organic phases dried and evaporated to give an oil which was subjected to purification by column chromatography (silica gel; ethyl acetate and heptane) giving an oil which precipitated as the oxalate salt (0.36 g) from acetone. LC/MS (m/z) 392 (MH+), RT = 1.92, purity: 99%.

In a similar manner the following compounds were prepared:

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}-6-(thiophen-2-yl)-4-trifluoromethylnicotinonitrile, **1b:** LC/MS (m/z) 514 (MH+), RT = 2.54, purity: 100%.

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}pyridine, **1c:** LC/MS (m/z) 339 (MH+), RT = 1.58, purity: 83%.

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}-6-methylnicotinonitrile, **1d:** LC/MS (m/z) 378 (MH+), RT = 1.95, purity: 92%.

3-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-2-chloropyridine, **1e:** LC/MS (m/z) 357 (MH+), RT = 1.50, purity: 93%.

3-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-2-bromopyridine, **1f:** LC/MS (m/z) 403 (MH+), RT = 1.54, purity: 89%.

3-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-2-methylpyridine, **1g:** LC/MS (m/z) 337 (MH+), RT = 0.71, purity: 78%.

3-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-5-chloropyridine, **1h:** LC/MS (m/z) 357 (MH+), RT = 1.58, purity: 100%.

2-{4-[4-(1H-Indol-4-yl)piperazin-1-yl]butylsulfanyl}-5-trifluoromethylpyridine, **1i:** LC/MS (m/z) 435 (MH+), RT = 2.14, purity: 80%.

2-{4-[4-(1H-Indol-4-yl)piperazin-1-yl]butylsulfanyl}-4,6-dimethylnicotinonitrile, **1j:** LC/MS (m/z) 420 (MH+), RT = 2.07, purity: 75%.

2-{3-[4-(1H-Indol-4-yl)piperazin-1-yl]propylsulfanyl}-5-trifluoromethylpyridine, **1k:** LC/MS (m/z) 421 (MH+), RT = 2.06, purity: 98%.

2-{3-[4-(1H-Indol-4-yl)piperazin-1-yl]propylsulfanyl}-4,6-dimethylnicotinonitrile, **1l:** LC/MS (m/z) 406 (MH+), RT = 1.99, purity: 100%.

Example 2

2-[4-(1H-Indol-4-yl)-piperazin-1-yl]-ethanethiol

1-(1*H*-Indol-4-yl)piperazine (3.9 g) and thiirane (1.75 g) was dissolved in DMF (200 mL) and refluxed for 1 h. The mixture was evaporated and re-dissolved in THF, dried with $MgSO_4$, filtered and evaporated to give the an oil which was subjected to purification by column chromatography (silica gel; ethyl acetate and heptane) giving the title compound as an oil (2,2 g). MS m/z (%): 261 (MH+, 100%), 202 (100%), 159 (23%).

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl-ethylsulfanyl}-6-methylnicotinonitrile, **2a.**

2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethanethiol (2.2 g) was dissolved in a solution of potassium *tert*-butoxide (0.81 g) in DMF (25 mL), stirred for 15 min and heated to 50 °C. A solution of 6-methyl-2-chloronicotinonitrile (1.91 g) in DMF (25 mL) was added drop wise and stirring was continued for another 2 h at 50 °C. The mixture was evaporated and re-dissolved in THF, washed with brine, dried with $MgSO_4$, filtered and evaporated to give an oil which was subjected to purification by column chromatography (silica gel; ethyl acetate, heptane and triethyl amine) giving the title compound as an oil which precipitated as the oxalate salt from acetone. . LC/MS (m/z) 396 (MH+), RT = 1.46, purity: 91%.

In a similar manner the following compounds were prepared:

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}nicotinonitrile, **2b:** LC/MS (m/z) 364 (MH+), RT = 1.66, purity: 96%.

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}-4-methylpyridine, **2c:** LC/MS (m/z) 353 (MH+), RT = 1.70, purity: 87%.

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}-4-methyl-6-(piperidin-1-yl)nicotinonitrile, **2d:** LC/MS (m/z) 461 (MH+), RT = 2.29, purity: 95%.

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}-4-trifluoromethyl-6-cyclopropylnicotinonitrile, **2e:** LC/MS (m/z) 472 (MH+), RT = 2.33, purity: 94%.

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}-3-methanesulfonyl-4-methyl-6-phenylpyridine, **2f:** LC/MS (m/z) 507 (MH+), RT = 2.16, purity: 92%.

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}nicotinonitrile, **2g:** LC/MS (m/z) 348 (MH+), RT = 1.46, purity: 88%.

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-4-methylpyridine, **2h:** LC/MS (m/z) 337 (MH+), RT = 1.66, purity: 100%.

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-6-methylnicotinamide, **2i:** LC/MS (m/z) 380 (MH+), RT = 1.41, purity: 96%.

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-4-methyl-6-(piperidin-1-yl)nicotinonitrile, **2j:** LC/MS (m/z) 445 (MH+), RT = 2.24, purity: 100%.

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-4-trifluoromethyl-6-cyclopropylnicotinonitrile, **2k:** LC/MS (m/z) 456 (MH+), RT = 2.20, purity: 100%.

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-3-methanesulfonyl-4-methyl-6-phenylpyridine, **2l:** LC/MS (m/z) 491 (MH+), RT = 2.16, purity: 70%.

6-Chloro-2-{2-[4-(1H-indol-4-yl)piperazin-1-yl]ethylsulfanyl}-4-methylnicotinonitrile, **2m:** LC/MS (m/z) 413 (MH+), RT = 2.00, purity: 69%.

6-Chloro-5-fluoro-2-{2-[4-(1H-indol-4-yl)piperazin-1-yl]ethylsulfanyl}nicotinonitrile, **2n:** LC/MS (m/z) 417 (MH+), RT = 1.91, purity: 85%.

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}pyrimidine, **2o:** LC/MS (m/z) 368 (MH+), RT = 1.62, purity: 73%.

5-Cyano-4-{2-[4-(1H-indol-4-yl)piperazin-1-yl]ethylsulfanyl}pyrimidine, **2p:** LC/MS (m/z) 365 (MH+), RT = 1.62, purity: 90%.

5-Cyano-4-{2-[4-(1H-indol-4-yl)piperazin-1-yl]ethylsulfanyl}-6-methylsulfanyl-2-phenylpyrimidine, **2q:** LC/MS (m/z) 488 (MH+), RT = 2.49, purity: 93%.

5-Ethyl-2-{2-[4-(1H-indol-4-yl)piperazin-1-yl]ethylsulfanyl}pyrimidine, **2r**: LC/MS (m/z) 368 (MH+), RT = 1.79, purity: 72%.

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}-4-trifluoromethylpyrimidine, **2s**: LC/MS (m/z) 408 (MH+), RT = 1.91, purity: 79%.

Pharmacological Testing

The affinity of the compounds of the invention to 5-HT_{1A} receptors was determined by measuring the inhibition of binding of a radioactive ligand at 5-HT_{1A} receptors as described in the following test:

Inhibition of ^{3}H-5-CT Binding to Human 5-HT_{1A} Receptors.

By this method, the inhibition by drugs of the binding of the 5-HT_{1A} agonist

^{3}H-5-carboxamido tryptamine (^{3}H-5-CT) to cloned human 5-HT_{1A} receptors stably expressed in transfected HeLa cells (HA7) (Fargin, A. et al. *J. Biol. Chem.* **1989**, *264*, 14848) is determined *in vitro*. The assay was performed as a modification of the method described by Harrington, M.A. et al. *J. Pharmacol. Exp. Ther.* **1994**, *268*, 1098. Human 5-HT_{1A} receptors (40 µg of cell homogenate) were incubated for 15 minutes at 37 °C in 50 mM Tris buffer at pH 7.7 in the presence of ^{3}H-5-CT. Non-specific binding was determined by including 10 µM of metergoline. The reaction was terminated by rapid filtration through Unifilter GF/B filters on a Tomtec Cell Harvester. Filters were counted in a Packard Top Counter. Compounds 1d, 2b, 2e and 2o were tested and showed IC_{50} values of less than 50 nM.

The compounds of the invention have also been tested for their effect on re-uptake of serotonin in the following test:

Inhibition of ^{3}H-5-HT Uptake Into Rat Brain Synaptosomes.

Using this method, the ability of drugs to inhibit the accumulation of ^{3}H-5-HT into whole rat brain synaptosomes is determined *in vitro*. The assay was performed as described by Hyttel, J. *Psychopharmacology* **1978**, *60,* 13. Compounds 1a, 1d, 1l, 2b, 2e and 2o were tested and showed IC_{50} values of less than 20 nM.

The 5-HT_{1A} antagonistic activity of some of the compounds of the invention has been estimated *in vitro* at cloned 5-HT_{1A} receptors, stably expressed in transfected HeLa cells (HA7). In this test, 5-HT_{1A} antagonistic activity is estimated by measuring the ability of the compounds to antagonize the 5-HT induced inhibition of forskolin induced cAMP accumulation. The assay was performed as a modification of the method described by Pauwels, P.J. et al. *Biochem. Pharmacol.* **1993**, *45*, 375. Compounds 1a, 1d, 1l, 2b and 2e were tested and showed IC_{50} values of less than 7000 nM.

Some of the compounds of the invention have also been tested for their *in vivo* effect on 5-HT_{1A} receptors in the assay described by Sánchez. C. et al. *Eur. J. Pharmacol.* **1996**, *315, pp 245*. In this test, antagonistic effects of test compounds are determined by measuring the ability of the test compounds to inhibit 5-MeO-DMT induced 5-HT syndrome.

The compounds of the present invention possess valuable activity as serotonin re-uptake inhibitors and have antagonistic effect at 5-HT_{1A} receptors. The compounds of the invention are therefore considered useful for the treatment of diseases and disorders responsive to the inhibition of serotonin re-uptake and antagonistic activity at 5-HT_{1A} receptors. Diseases responsive to the inhibition of serotonin re-uptake are well-known in the art and include affective disorders, such as depression, psychosis, anxiety disorders including general anxiety disorder, panic disorder, obsessive compulsive disorder, etc.

As explained above, the antagonistic activity at 5-HT_{1A} receptors of the compounds of the invention will counteract the negative feed back mechanism induced by the inhibition of serotonin reuptake and is thereby expected to improve the effect of the serotonin reuptake inhibiting activity of the compounds of the invention.

The compounds as claimed herein are therefore considered to be particularly useful as fast onset of action medicaments for the treatment of depression. The compounds may also be useful for the treatment of depressions which are non-responsive to currently available SSRIs.

Some of the compounds of the invention have also been found to have affinity to dopamine D_3 and D_4 receptors in the following two assays.

Inhibition of the binding of ^{3}H-YM-09151-2 to human dopamine D_4 receptors

By this method, the inhibition by drugs of the binding of [^{3}H]YM-09151-2 (0.06 nM) to membranes of human cloned dopamine $D_{4.2}$ receptors expressed in CHO-cells is determined *in vitro*. Method modified from NEN Life Science Products, Inc., technical data certificate PC2533-10/96.

Inhibition of the binding of [^{3}H]-Spiperone to human D_3 receptors

By this method, the inhibition by drugs of the binding [^{3}H]Spiperone (0.3 nM) to membranes of human cloned dopamine D_3-receptors expressed in CHO-cells is determined

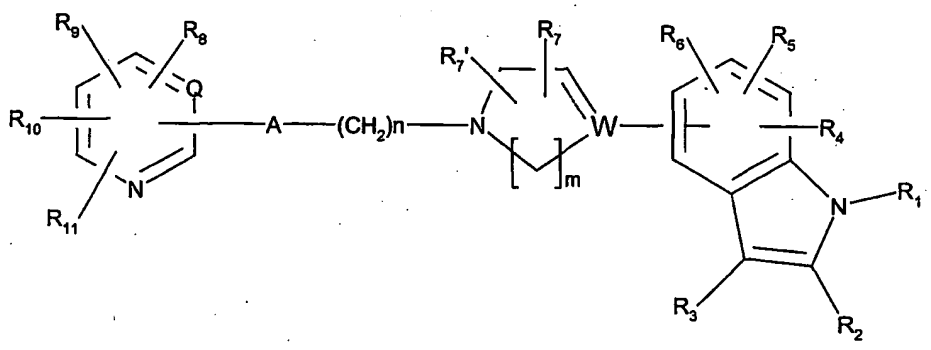
in vitro. Method modified from R.G. MacKenzie et al. *Eur. J. Pharm.-Mol. Pharm. Sec.* **1994**, *266*, 79-85.

Some of the compounds of the invention have also been tested for their *in vivo* effect on 5-HT_{1A} receptors in the assay described by Sánchez, C. et al. *Eur. J. Pharmacol.* **1996**, *315*, pp 245. In this test, antagonistic effects of test compounds are determined by measuring the ability of the test compounds to inhibit 5-MeO-DMT induced 5-HT syndrome.

Accordingly, as the compounds of the invention show affinities in the described tests, they are considered useful in the treatment of affective disorders, such as depression, generalised anxiety disorder, panic disorder, obsessive compulsive disorders, social phobia and eating disorders, and neurological disorders such as psychosis.

Claims:

1. A compound represented by the general formula I



I

wherein

A represents O or S;

n is 2, 3, 4, 5, 6, 7, 8, 9 or 10;

m is 2 or 3;

W represents N, C or CH;

Q represents N, C or CH;

and the dotted line represents an optional bond;

R^1 represents hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, aryl-C_{1-6}-alkyl or acyl;

R^2, R^3, R^4, R^5 and R^6 independently represent hydrogen, halogen, cyano, nitro, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylsulfanyl, C_{1-6} alkylsulfonyl, hydroxy, hydroxy-C_{1-6}-alkyl, C_{1-6}-alkoxycarbonyl, acyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, trifluoromethyl, trifluoromethoxy, $NR^{15}R^{16}$ wherein R^{15} and R^{16} independently represent hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or phenyl; or R^{15} and R^{16} together with the nitrogen to which they are attached form a 5- or 6-membered ring optionally containing one further heteroatom;

R^7 and $R^{7'}$ independently represent hydrogen or C_{1-6}-alkyl or may together form a bridge consisting of two or three methylene groups;

R^8, R^9, R^{10} and R^{11} are each independently selected from hydrogen, halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, phenyl, thiophenyl, C_{1-6}-alkoxy, C_{1-6}-alkylsulfanyl, C_{1-6}-alkylsulfonyl, hydroxy, formyl, acyl, acylamino, aminocarbonyl, C_{1-6}-alkoxycarbonylamino, aminocarbonylamino, C_{1-6}-alkylaminocarbonylamino and di(C_{1-6}-alkyl)amino-carbonylamino, $NR^{13}R^{14}$ wherein R^{13} and R^{14} independently represent hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or phenyl; or R^{13} and R^{14} together with the nitrogen to which they are attached form a 5- or 6-membered ring optionally containing one further heteroatom;

its enantiomers and a pharmaceutically acceptable acid addition salt thereof.

2. The compound of formula (I) of claim **1**, wherein n is 2, 3 or 4.

3. The compound of formula (I) according to any of claims **1 to 2**, wherein W represents N.

4. The compound of formula (I) according to any of claims **1 to 3**, wherein R^7 and $R^{7'}$ are both hydrogen.

5. The compound of formula (I) according to any of claims **1 to 4**, wherein R^1 is hydrogen.

6. The compound of formula (I) according to any of claims **1 to 5**, wherein R^2, R^3, R^4, R^5 and R^6 represent hydrogen.

7. The compound of formula (I) according to any of claims **1 to 6**, wherein R^8, R^9, R^{10} and R^{11} independently represent hydrogen, halogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, CN, CF_3, OCF_3, NH_2, $NR^{13}R^{14}$ wherein R^{13} and R^{14} independently represent hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or phenyl; or R^{13} and R^{14} together with the nitrogen form a piperidine or pyrrolidine.

8. The compound of formula (I) according to claim **7**, wherein R^8, R^9, R^{10} and R^{11} independently represent methyl, cyclopropyl, trifluoromethyl, cyano, chloro, bromo,

piperidinyl, phenyl.

9. The compound of formula I according to any of the preceding claims, said compound being:

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}-4,6-dimethylnicotinonitrile, 1a,
2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}-6-(thiophen-2-yl)-4-trifluoromethylnicotinonitrile, 1b,
2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}pyridine, 1c,
2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}-6-methylnicotinonitrile, 1d,
3-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-2-chloropyridine, 1e,
3-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-2-bromopyridine, 1f,
3-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-2-methylpyridine, 1g,
3-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-5-chloropyridine, 1h,
2-{4-[4-(1H-Indol-4-yl)piperazin-1-yl]butylsulfanyl}-5-trifluoromethylpyridine, 1i,
2-{4-[4-(1H-Indol-4-yl)piperazin-1-yl]butylsulfanyl}-4,6-dimethylnicotinonitrile, 1j,
2-{3-[4-(1H-Indol-4-yl)piperazin-1-yl]propylsulfanyl}-5-trifluoromethylpyridine, 1k,
2-{3-[4-(1H-Indol-4-yl)piperazin-1-yl]propylsulfanyl}-4,6-dimethylnicotinonitrile, 1l,
2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}-6-methylnicotinamide, 2a,
2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}nicotinonitrile, 2b,
2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}-4-methylpyridine, 2c,
2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}-4-methyl-6-(piperidin-1-yl)nicotinonitrile, 2d,
2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}-4-trifluoromethyl-6-cyclopropylnicotinonitrile, 2e,
2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}-3-methanesulfonyl-4-methyl-6-phenylpyridine, 2f,
2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}nicotinonitrile, 2g,
2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-4-methylpyridine, 2h,
2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-6-methylnicotinamide, 2i,
2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-4-methyl-6-(piperidin-1-yl)nicotinonitrile, 2j,
2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-4-trifluoromethyl-6-cyclopropylnicotinonitrile, 2k,

2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethoxy}-3-methanesulfonyl-4-methyl-6-phenylpyridine, 2l,
6-Chloro-2-{2-[4-(1H-indol-4-yl)piperazin-1-yl]ethylsulfanyl}-4-methylnicotinonitrile, 2m,
6-Chloro-5-fluoro-2-{2-[4-(1H-indol-4-yl)piperazin-1-yl]ethylsulfanyl}nicotinonitrile, 2n,
4,6-Dimethyl-2-{2-[4-(1H-indol-4-yl)piperazin-1-yl]ethylsulfanyl}pyrimidine, 2o,
5-Cyano-4-{2-[4-(1H-indol-4-yl)piperazin-1-yl]ethylsulfanyl}pyrimidine, 2p, or
5-Cyano-4-{2-[4-(1H-indol-4-yl)piperazin-1-yl]ethylsulfanyl}-6-methylsulfanyl-2-phenylpyrimidine, 2q,
5-Ethyl-2-{2-[4-(1H-indol-4-yl)piperazin-1-yl]ethylsulfanyl}pyrimidine, 2r
2-{2-[4-(1H-Indol-4-yl)piperazin-1-yl]ethylsulfanyl}-4-trifluoromethylpyrimidine, 2s

or a pharmaceutical acceptable salt thereof.

10. A pharmaceutical composition comprising at least one compound of Formula I according to claims **1-9**, or a pharmaceutically acceptable acid addition salt thereof or prodrug thereof in a therapeutically effective amount and in combination with one or more pharmaceutically acceptable carriers or diluents.

11. The use of a compound according to any of the claims **1 to 9**, or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of a disorder or disease responsive to the combined effect of inhibition of serotonin uptake and antagonism of 5-HT_{1A} receptors.

12. The use of a compound according to any of the claims **1 to 9**, or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of a disorder or disease responsive to the combined effect of 5-HT_{1A} receptors and dopamine D_4 receptors.

13. The use according to any of the claims **11 to 12**, wherein the diseases and disorders are generalised anxiety disorder, panic disorder, obsessive compulsive disorder, depression, social phobia, eating disorders, and neurological disorders such as psychosis.

14. A method for the treatment of a disorder or disease of living animal body, including a human, which is responsive to the effect of inhibition of serotonin uptake and antagonism

of 5-HT_{1A} receptors comprising administering to such a living animal body, including a human, a therapeutically effective amount of a compound according to claims **1 to 9** or a pharmaceutically acceptable acid addition salt thereof.

15. A method for the treatment of a disorder or disease of living animal body, including a human, which is responsive to the effect of 5-HT_{1A} and D_4 receptors comprising administering to such a living animal body, including a human, a therapeutically effective amount of a compound according to claims **1 to 9** or a pharmaceutically acceptable acid addition salt thereof.

16. A method of treatment according to claim **14 to 15** where the disorder or disease is an affective disorder such as general anxiety disorder, panic disorder, obsessive compulsive disorder, depression, social phobia and eating disorders, or a neurological disorder such as psychosis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 02/00436

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 401/12, C07D 403/12, A61K 31/497, A61K 31/506
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9955672 A2 (AMERICAN HOME PRODUCTS CORPORATION), 4 November 1999 (04.11.99) --	1-13
A	EP 0900792 A1 (DUPHAR INTERNATIONAL RESEARCH B.V.), 10 March 1999 (10.03.99) --	1-13

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 October 2002	09 -10- 2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer GÖRAN KARLSSON/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK02/00436

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 14-16
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/DK 02/00436

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9955672 A2	04/11/99	AU 3667899 A	16/11/99
		CA 2330452 A	04/11/99
		CN 1307562 T	08/08/01
		EP 1076647 A	21/02/01
		JP 2002513001 T	08/05/02
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